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PRESS RELEASE

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Customised cells to fight brain cancer

Scientists at UNIGE and HUG have created artificial immune cells capable of recognising and destroying glioblastoma cells.

With a five-year survival rate of less than 5%, glioblastoma is one of the most aggressive types of brain cancer. Until now, all available treatments, including immunotherapy — which involves strengthening the immune system to fight cancer— have proved disappointing. CAR-T cells are genetically modified immune cells manufactured in the laboratory and designed to identify and destroy cancer cells. By targeting a protein present in the tumour environment, a team from the University of Geneva (UNIGE) and the Geneva University Hospital (HUG) has developed CAR-T cells capable of destroying glioblastoma cells. Their efficacy in an animal model of the disease paves the way for clinical trials in humans. These results are published in the *Journal for ImmunoTherapy of Cancer*.

Glioblastoma presents as a mass in the brain, consisting of tumour cells but also other types of cells, as is the case in most cancers. "However, glioblastoma is unique in that it contains very few T cells, the immune cells that are able to recognise cancer cells and destroy them," says Valérie Dutoit, a researcher in the Department of Medicine and the Translational Research Centre in Onco-Haematology (CRTOH) at the UNIGE Faculty of Medicine. "This is why glioblastoma, unlike melanoma or certain lung cancers, for example, does not respond to standard immunotherapies. Our approach is therefore to provide the patient with the missing T cells by generating them in the laboratory."

High-precision cells

The production of CAR-T cells (for chimeric antigen receptor T cells) involves taking T cells from the blood of the patient, modifying them in the laboratory to enable them to identify and destroy tumour cells, and then re-injecting them. "This approach is based on identifying tumour-specific proteins that T cells can target without affecting healthy cells, a task that is particularly complex in the case of glioblastoma, which is characterised by a high cellular heterogeneity," explains Denis Migliorini, professor in the Department of Medicine and at the CRTOH of the UNIGE Faculty of Medicine and head of the neuro-oncology unit at the HUG. "In a previous study, we identified an important target, the PTPRZ1 marker, which is present on the surface of certain tumour cells. However, attacking glioblastoma on a single target is not enough to avoid the risk of relapse."

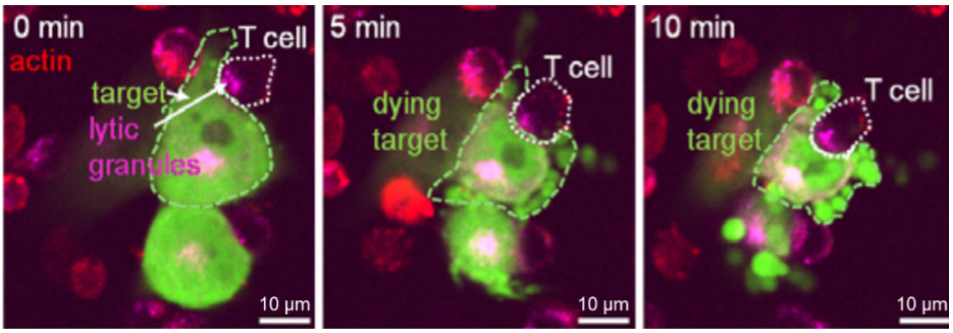
The team is now strengthening its arsenal with a new target associated with glioblastoma: the Tenascin-C (TNC) protein, produced and released into the tumour environment. It constitutes the extracellular matrix – a kind of jelly in which tumour cells are immersed. By targeting Tenascin-C, CAR-T cells trigger a series of pro-inflammatory reactions that induce the death of the cells that

produce it. “Furthermore, we have been able to demonstrate that CAR-T cells are capable of locally destroying cancer cells that do not produce Tenascin-C, which amplifies their activity without any risk of deleterious effects on healthy cells,” says Denis Migliorini.

Overcoming tumour resistance

One of the problems encountered by scientists is the emergence of resistance mechanisms, which lead to the rapid exhaustion of CAR-T cells. “By identifying three markers of cell exhaustion and counteracting their activity, we were able to significantly prolong the efficacy of CAR-T cells in mice with glioblastoma used as models of the human disease,” enthuses Valérie Dutoit.

The very positive results of this study now make it possible to consider a clinical trial. “Our goal is to generate genetically modified immune cells against several targets at once in the hope of reaching as many cancer cells as possible,” says Denis Migliorini. This clinical study is expected to begin in about a year and will take place in Geneva and Lausanne. “It will also involve adjusting CAR-T cells to each patient in order to eradicate as many cells as possible, even when facing tumour heterogeneity.”



A real-time imaging experiment (images taken at 0, 5 and 10 minutes) shows a CAR-T cell in contact with a glioblastoma cell (artificially marked in green). This contact causes the CAR-T cell to concentrate granules (lytic granules, shown in pink) containing the proteins necessary for the death of the target cell. © Denis Migliorini

High resolution pictures

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